Evaluation of the contribution of individual gene groups to a 17-gene prognostic prostate cancer signature.

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Background: A 17-gene biopsy-based RT-PCR assay (Oncotype DX Prostate Assay) has been validated as a predictor of adverse pathology and biochemical recurrence (BCR) in clinically very low to intermediate-risk prostate cancer patients. The assay measures expression of 12 cancer and 5 reference genes that are combined to calculate a Genomic Prostate Score (GPS; scaled 0-100), providing a biologic measure of tumor aggressiveness. The cancer genes represent four biological pathways: androgen signaling, stromal response, cellular organization and proliferation. We examined the effects of variation in quantitative expression of individual gene groups on GPS results and prediction of clinical risk. Methods: The first 3,500 tumor specimens processed in the Genomic Health Inc.'s reference laboratory were included. Expression of individual genes was measured and expression of the four gene groups and GPS calculated. For each gene group, GPS of patients with the lowest 5% expression levels were contrasted with GPS of patients with highest 5% expression levels. Results: Percentages of NCCN very low, low and intermediate patients were 28%, 37%, 30%; median age was 65. Mean and median GPS were 24.6 (SD 12.0) and 23 (range 0-90). Individual gene groups exhibited wide expression ranges (e.g. proliferation-16-fold difference (FD) vs. cellular organization > 8000 FD). Large differences in expression of each gene group were reflected in GPS values and, based on a prior clinical validation study, translate into large differences in BCR risk (Table). Conclusions: Each of the four gene groups show large variations in expression, meaningfully affect the GPS, and contribute to the prediction of PCa aggressiveness.

Gene groups	Median GPS for lowest 5% of expression (1st, 3rd quartiles)	Predicted 5-year BCR risk for median GPS for lowest 5% of expression [95% CI]	Median GPS for highest 5% of expression (1st, 3rd quartiles)	I
Stromal	12 (8, 19)	6% [3%, 10%]	43 (34, 53)	
Cell organization	37 (27, 46)	20% [15%, 25%]	21 (15, 27)	
Androgen	50 (44, 58)	36% [27%, 46%]	9 (5, 13)	
Proliferation	16 (11, 22)	7% [4%, 11%]	35 (26, 43)	